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Hypoalbuminemia: Pathogenesis and Clinical Significance

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Abstract

Hypoalbuminemia is associated with inflammation. Despite being addressed repeatedly in the literature, there is still confusion regarding its pathogenesis and clinical significance. Inflammation increases capillary permeability and escape of serum albumin, leading to expansion of interstitial space and increasing the distribution volume of albumin. The half-life of albumin has been shown to shorten, decreasing total albumin mass. These 2 factors lead to hypoalbuminemia despite increased fractional synthesis rates in plasma. Hypoalbuminemia, therefore, results from and reflects the inflammatory state, which interferes with adequate responses to events like surgery or chemotherapy, and is associated with poor quality of life and reduced longevity. Increasing or decreasing serum albumin levels are adequate indicators, respectively, of improvement or deterioration of the clinical state. In the interstitium, albumin acts as the main extracellular scavenger, antioxidative agent, and as supplier of amino acids for cell and matrix synthesis. Albumin infusion has not been shown to diminish fluid requirements, infection rates, and mortality in the intensive care unit, which may imply that there is no body deficit or that the quality of albumin "from the shelf" is unsuitable to play scavenging and antioxidative roles. Management of hypoalbuminaemia should be based on correcting the causes of ongoing inflammation rather than infusion of albumin. After the age of 30 years, muscle mass and function slowly decrease, but this loss is accelerated by comorbidity and associated with decreasing serum albumin levels. Nutrition support cannot fully prevent, but slows down, this chain of events, especially when combined with physical exercise. (*JPEN J Parenter Enteral Nutr.* 2019;43:181–193)

Keywords

capillary permeability; fractional synthesis rate albumin; growth; hypoalbuminemia; immune response; inflammation; interstitial space; pregnancy; puberty; serum albumin binding protein; serum albumin indicator of inflammatory activity; albumin infusion; albumin mass; serum albumin risk factor; albumin scavenger; vascular endothelial growth factor

Introduction

Hypoalbuminemia is common in clinical practice, and serum albumin levels are often routinely measured in severely ill or malnourished patients. Although hypoalbuminemia may develop within hours in acute disease or after trauma and resuscitation in previously well-nourished individuals and is also present in chronic inflammatory diseases despite adequate nutrition intake, it is often wrongly considered to be an indicator of inadequate nutrition intake that can be relieved by nutrition support alone. There is actually a poor correlation between the level of nutrition intake and the serum albumin level. For example, anorexia nervosa patients have normal or only slightly decreased serum albumin levels despite very low nutrition intake, unless infected or traumatized. Many anorexia nervosa patients have a body mass index <18 kg/m^2 and have low muscle mass and strength, but they are otherwise functioning relatively well.[1] Further, patients with chronic diseases and hypoalbuminemia lose fat-free mass, considered to be an essential indicator of the undernourished state, despite adequate food intake.[2,3] Rather than reflecting undernutrition per se, hypoalbuminemia is more a reflection of the extent of physiologic stress resulting from disease or trauma-related inflammation. These considerations do not

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exclude the likelihood that hypoalbuminemia often coincides with a negative nutrient balance for which nutrition support is indicated.

The objectives of this semicomprehensive review are to define the pathophysiology of hypoalbuminemia associated with increases in capillary permeability and altered kinetics of serum albumin in inflammatory states, including states of physiologic or pathologic growth. In addition, the potentially beneficial role of these changes will be highlighted as well as the significance of increasing or decreasing serum albumin levels as indicators of improvement or deterioration of the clinical state. Finally, the significance of hypoalbuminemia as a risk indicator of negative outcome after medical treatment or of diminished longevity will be discussed.

In view of the many areas of pathophysiology addressed, we will limit the number of references to subjects that are not commonly accepted knowledge. In this area, very few randomized trials and meta-analyses have been performed. Much of the material in this paper regards the pathophysiology of inflammation at the whole-body level and recent, more in-depth papers on cell biology and the beneficial intracellular and extracellular role of albumin.

The Pathophysiology Underlying Hypoalbuminemia

Hypoalbuminemia is largely a function of increased vascular permeability and increased interstitial volume. In this section we will discuss the role of inflammation in mediating these responses, not only in pathologic states, but also in life events such as pregnancy, lactation, and cancer growth.

Inflammation, Increased Capillary Permeability, and Hypoalbuminemia

Increased vascular permeability for cells and plasma solutes is a universal reaction in trauma, critical illness, chronic disease, life events, multiple or isolated organ failure, and cancer. This response is evident in circumstances including edema in healing wounds and the necessity to maintain intravascular volume by "overhydrating" traumatized or postsurgery patients. Adequately resuscitated patients are maintained in a positive fluid balance of 5–10 liters after clean elective major surgery or other types of trauma.[4] Fluid resuscitation is necessary in these circumstances to avoid hypovolemia and the development of shock. The same happens in children after burns, where fluid balance is positive despite the effort to prevent overhydration.[5] The fact that fluid retention inevitably and visibly occurs in wounds as well as at the whole-body level after trauma and burns could reflect that this response is beneficial to some extent, but may become harmful when the inflammatory stimulus cannot be adequately overcome or treated.[6,7] In wounds, virtually every type of immune cell appears, producing cytokines and growth factors that support the healing process. Increased cytokine expression does not only happen after trauma or infection, but also in physiologic states including pregnancy and other situations where increased cell proliferation and matrix deposition are required.[8-10]

In acute wounds or infected areas, repair is stimulated by proinflammatory and inflammatory cytokines, and visible wound edema occurs due to expansion of the interstitial space (Figure 1). Both phases of cytokine and growth factor expression support different inflammatory processes. In the initial proinflammatory phase, the affected area is prepared for repair via removing debris by macrophages, promoting angiogenesis, and increasing permeability. In this phase, there is a preponderance of Th1 helper cell–induced cytokine and growth factor release. Importantly, debris and products of damage or infection are cleared, preparing the affected areas for repair. In the subsequent anti-inflammatory phase, healing mechanisms prevail with important stimulatory roles for Th2 helper cell activity. When this phase is successful, inflammation has been shown to resolve slowly in the course of months, promoted at least in part by lipid-derived mediators.[11] From the start of the insult, platelet-derived growth factor in acute wounds and interleukin (IL)-6 and nitric oxide (NO)-induced vascular endothelial growth factor (VEGF) in all other inflammatory states are highly expressed (Table 1). They induce an increase of capillary permeability and angiogenesis, in turn promoting entry of cells and plasma solutes, such as albumin, fibrinogen, immunoglobulins, electrolytes, and nutrients into wounds and growing tissues. Other sites (muscle and adipose tissue in collaboration with the liver and, possibly, the kidney[12]) release these solutes into the vascular compartment from where they enter the extravascular extracellular compartment (interstitium) at increased rates, also facilitated by the increased capillary permeability.[4,13-17] The interstitial space, plasma volume, and cell mass constitute the distribution volume of several solutes including serum albumin, as well as other proteins and electrolytes. Due to cycling of these substrates between these spaces, their expansion has a lowering effect on substrate concentrations. Immune cells and platelets swell in sepsis, but not much is known regarding myocytes, adipocytes, hepatocytes, etc. However, abundant clinical evidence exists showing that after severe trauma or sepsis, fat-fee mass increases 5–15 liters or even more.[4] Total and extracellular water, sodium, and chloride content of muscle have been found to increase after injury, and despite nutrition, while muscle potassium and magnesium decrease.[18,19] In studies in patients with liver cirrhosis, decreased total body potassium and creatinine excretion were found, correlating with the results of bioelectrical impedance analysis, while body weights were relatively well preserved due to water retention.[20]

Albumin can enter cells and cell organelles, but the kinetics of this process are not quantified. However, in

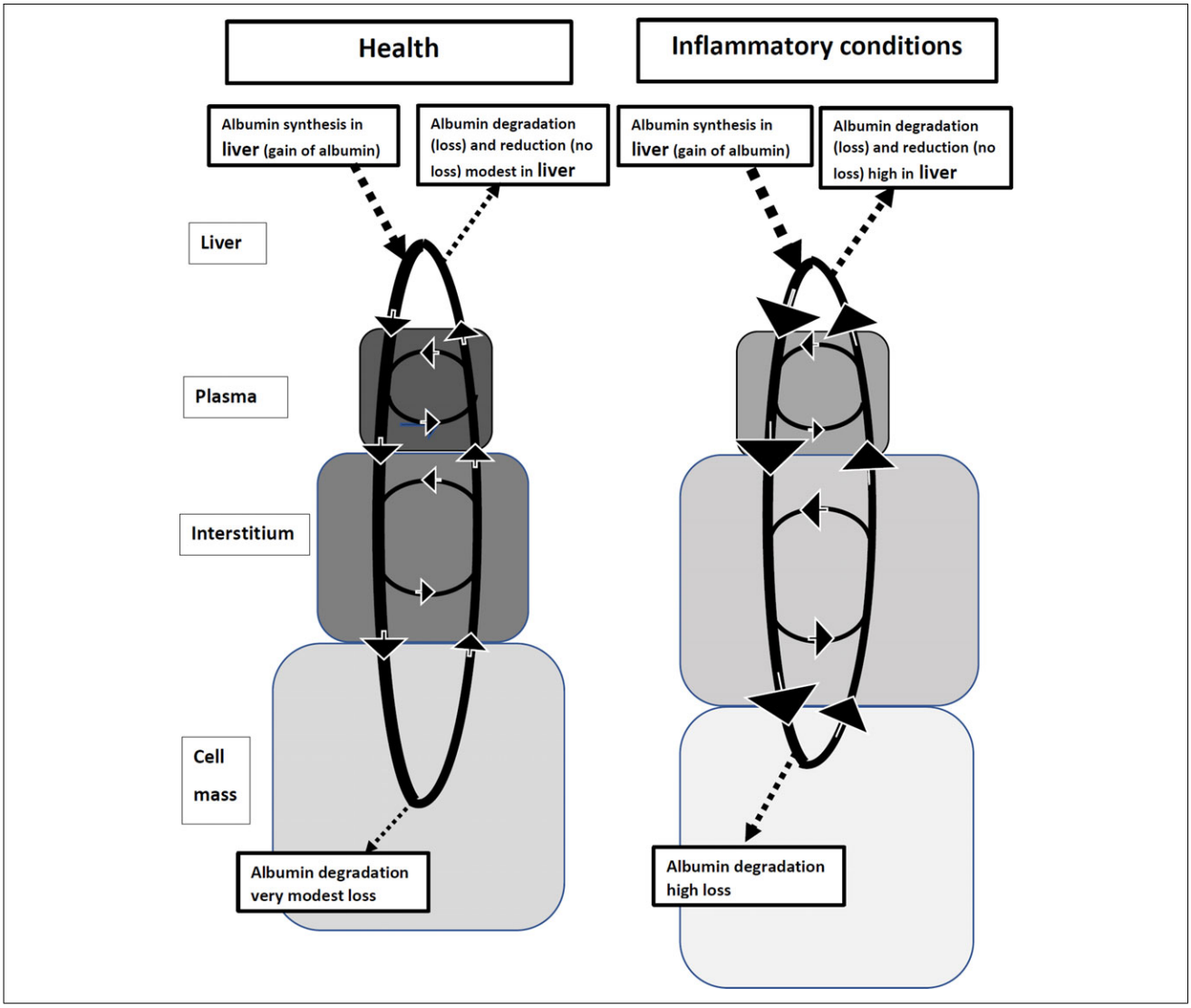

Figure 1. Schematic representation of albumin flux, synthesis, and degradation.
Solid arrows: transmembrane transport. **Dashed arrows:** Synthesis in liver; **Degradation:** intracellular proteolysis. **Gain:** Increase in total body albumin. **Loss:** decrease in total body albumin. **Reduction:** reducing oxidized total boyd albumin. The length of the black oval represents albumin mass, which is diminished due to more rapid intracellular breakdown in liver and proliferating cells. It is uncertain, whether cell volume is stable, while it is certain that cell solids are decreased in inflammatory conditions. Fluxes are represented by the size of arrows crossing the cell walls between liver, plasma, interstitium, and cell. They are larger (higher transmembrane flux) in inflammation than in health. It is possible that only a part of the flux entering the interstitium enters the cell, but rather (especially in inflammation after oxidation or scavenging) turns back to the plasma and is then reduced or degraded in the liver. The size of the quadrangles represents the volume of the different compartments and their grey intensity, the concentration of serum albumin. The size of cell mass in health and inflammatory states have been depicted to be identical although this is uncertain; cell mass may be increased, while cell solids are decreased. In health, net hepatic albumin output enters the plasma, and from there, it gets limited access to the interstitium at a low rate and, subsequently, to the cells. In these compartments, albumin serves as antioxidant and scavenger and to a very limited degree as supplier of amino acids for cell proliferation. Oxidized and otherwise damaged albumin is broken down in the liver or reduced for renewed antioxidation or scavenging. In inflammatory states, these functions are upregulated depending on the severity of the inflammatory insult, increasing fluxes from plasma to interstitium by increased capillary permeability. Albumin synthesis may increase, but oxidation of and scavenging by albumin will be upregulated. Similarly, albumin serves as intracellular amino acid donor for cell proliferation at a much higher rate than in health. Consequently, breakdown of albumin is higher in inflammatory states than in health, leading to decreased albumin mass despite potentially increased synthesis. These processes have been described in the literature, but have not been quantified. Transport into the cell as depicted in Figure 1 may be exaggerated and reentry of serum albumin from the interstitium into the plasma underestimated.

pharmacology, albumin is studied as a potential carrier of drugs. To prolong drug effects, methods have been explored to prolong their binding to albumin and to increase the half-life of albumin by binding to site-specific mutants of the neonatal Fc receptor (FcRn). In health, this receptor is bound to albumin and has been found to prolong the half-life of albumin while there is substantial cycling of serum albumin into and out of the cell,[21] but in disease states, FcRn downregulation shortens the half-life of albumin due to increased intracellular breakdown. This furnishes amino acids used as building blocks for increased cell proliferation. This occurs at a lower rate in health.[22]

Trauma, disease, growth, etc. are inflammatory conditions that are associated with hypoalbuminemia. More severe inflammation is associated with progressively lower serum albumin levels, although the strength of the correlation has only sparsely been investigated.[23,24] However, it is clinically evident that in severely septic patients, a persisting positive fluid balance and decreasing serum albumin levels after the start of sepsis spell doom. Changing to a negative fluid balance (polyuria), rising serum albumin levels signal recovery. There is a highly significant correlation between serum albumin level and mortality risk when stratified for age and gender.[25]

In the literature, expansion of interstitial space is generally linked to increased transcapillary escape of plasma constituents into the interstitium, despite findings in experimental endotoxin-treated animals that lymphatic backflow from the interstitium is also increased.[26] Fibrinogen yields fibrin after leaving the vascular space due to the simultaneous escape of clotting factors. It has been suggested that this increases viscosity/oncotic pressure, inducing retention of water and, thereby, expanding interstitial space. To our knowledge, in this regard, the role of cells has not been assessed.

Inflammation and Tissue Growth

The inflammatory response and increased capillary permeability that are necessary for tissue healing after trauma or infection also occur in physiologic and pathologic growth. Thus, there is a mild and sustained inflammatory response in pregnancy.[10] The synthesis of cytokines and growth factors is mildly increased while exhibiting Th1 helper cell dominance, but is further upregulated and changed to Th2 helper cell dominance during fetal distress, and decreases when resulting in premature birth.[10,27,28] A similar pattern is observed for VEGF, stimulating angiogenesis and promoting capillary permeability,[29] leading to expansion of the interstitium.[30,31]

Cytokine and growth factor production is also increased when preparing for lactation, stimulating the development of the terminal end buds for lactation.[32] Similar factors are produced in mammary cancer growth to promote tumor invasiveness. Cancer tissue is riddled with immune cells which support tumor growth, while inflammation is also evident at the whole-body level.[33,34] Altogether, the inflammatory response is a general mechanism promoting accelerated cell proliferation and matrix deposition in all conditions in which this is required. An essential element consists of growth factor–induced (eg, VEGF) increases in vascular permeability. VEGF expression and increased vascular permeability occur in infection,[14,35] trauma,[15,16,36] during fetal and postnatal growth,[29,37-39] preparing for lactation,[39,40] cancer,[41,42] protein-losing enteropathy,[43] and nephrotic syndrome[44,45] (Table 1). The positive role of VEGF and its effect on angiogenesis and vascular permeability is supported by the evidence that treatment with anti-VEGF in renal cancer aggravates renal failure.[45,46]

The inference that acute inflammation usually has positive effects is strongly supported by the finding that inhibiting the inflammatory response by nonsteroidal anti-inflammatory drugs worsens wound and bone healing,[47-50] increases the risk of anastomotic failure or sepsis after surgery,[51,52] aggravates heart and renal failure,[53,54] interferes with an adequate immune response to antigen presentation in the intestine (leading to ulceration and bleeding),[55-58] and causes premature birth and cryptorchism in neonates.[58-62]

Hypoalbuminemia and Albumin Kinetics

Low serum albumin levels in malnourished or stressed individuals have often been considered to be caused by diminished synthesis. However, in most disease states in which synthesis rates have been measured, fractional synthesis rate (FSR) in plasma has been reported to be normal or mildly increased (Table 1).[63-71] FSR is only decreased in liver failure where synthetic rate is related to liver function[72] and possibly in children with kwashiorkor for unknown reasons.[73] While increased fractional and absolute synthesis rates in plasma seem incongruous with decreased levels of serum albumin, they may not reflect an increase in synthesis at the whole-body level. In addition, synthesis rate is just 1 of the factors determining total serum albumin mass in the body. Serum albumin mass is also influenced by the half-life of serum albumin. This has been rarely measured, but turnover time has been found to be shortened in hypertension, acromegaly, nephrotic syndrome, and protein-losing enteropathy.[65,74-76]

Synthesis rates in plasma have been shown to increase after nutrition support in healthy individuals. Whether this is also true in critically ill (septic) patients is uncertain. In postsurgical or septic children and adolescents, FSRs were high, but did not increase after nutrition support.[77] In intestinal fistula patients with intra-abdominal abscesses, serum albumin synthesis rate was found to be decreased.[78] This does not exclude the possibility that in individuals with mild disease activity, nutrition support, especially including protein/amino acids, increases serum albumin synthesis.

Table 1. Pathophysiology of Hypoalbuminemia in Disease and Life Events.

Disease/Life Event	Serum Albumin Concentration	Vascular Permeability	Serum Albumin Abs Synth	Serum Albumin Half-Life	Serum Albumin Total Mass	Distribution Volume	VEGF	Remarks
Growth from fetus to adult, lactation and molt								
Growth from child to adult	N ↓ rising to adult N	NA	NA	NA	NA	NA	↑[37,38,161161]	Connectivity VEGF gene-metabolic pathway stronger in children
Adult male vs female	Male N	NA	NA	NA	NA	NA	↑[161]	Menstrual cycle may elicit mild inflammatory activity
	Female N↓[112]	NA	NA	NA	NA	NA		
Pregnancy 1st, 2nd, 3rd trimester	↓ to ↓↓	↑ to↑↑	↑	NA	NA	↑ to↑↑	↑[29]	Increasing permeability and distribution volume in the course of pregnancy
Lactation	NA	↑ in breasts	NA	NA	NA	NA	↑[39,40,162]	VEGF operative in mammary gland development and lactation
Molt	↓[163]	NA	NA	NA	NA	NA	↑[164]	
Disease, infection, trauma, mono-organ failure, protein-losing syndromes, cancer								
Liver disease, Child A, B, or C	↓ to ↓↓↓	↑ to↑↑↑	↓ to ↓↓↓	↑ !!	↓ to ↓↓	↓ to ↓↓↓	↑[165]	VEGF upregulated in cancer; anti-VEGF treatment considered promising
Infection mild to severe	↓ to ↓↓↓	↑ to ↑↑↑	↑ to ↑↑↑	↓ to ↓↓↓	↓ to ↓↓↓	↑ to ↑↑↑[a]	↑[35]	Inflammatory course unpredictable due to bacterial interference
Trauma	↓ to ↓↓	↑ to↑↑	↑ to↑↑	↓ to ↓↓	NA	↑ to↑↑	↑[36]	Data in part from[4]
Mono-organ failure	↓ to ↓↓	NA	↑ to↑↑↑	↑ to↑↑↑			↑[91,166,167]	Data available in renal failure and myocardial infarction
Protein-losing enteropathy	↓ to ↓↓↓	↑ to↑↑↑	↑ to↑↑↑	↓ to ↓↓	↓ to ↓↓↓	↑ to↑↑↑	↑[43]	Albumin mass↓ due to protein loss and shortened half-life
Nephrotic syndrome	↓ to ↓↓↓	↑ to↑↑↑	↑ to↑↑↑	↓ to ↓↓	↓ to ↓↓↓	↑ to↑↑↑	↑[44,45]	Albumin mass↓ due to protein loss and shortened half-life
Cancer	↓ to ↓↓	↑ to↑↑	↑ to↑↑	↓ to ↓↓	↓ to ↓↓	↓ to ↓↓	↑[41,42]	Anti-VEGF beneficial in renal cancer but deleterious for kidney function

The kinetics of albumin are represented in states with low or low normal serum albumin levels, occurring during life events and stress conditions, such as disease, trauma, or organ failure. Hypoalbuminemia is proposed to result from increased capillary permeability and changes in albumin kinetics, necessary to allow substrates to reach areas with increased cell proliferation and matrix deposition. Of the different cytokines, growth factors, or hormones known to steer this beneficial metabolic response, the role of VEGF is emphasized, specifically promoting angiogenesis and capillary permeability and instrumental in this beneficial response. Albumin kinetics have not been thoroughly investigated in all conditions mentioned.

Data are in part obtained from Levitt and Levitt.[91]

Abs Synth, absolute synthesis; N, normal value; NA, data not available; VEGF, vascular endothelial growth factor; ↓, ↓↓, ↓↓↓, modestly, moderately, very much decreased; ↑, ↑↑, ↑↑↑, modestly, moderately, very much increased; N with arrow pointing downwards: normal value in the low range.

[a]Clinical judgement.

A change in the amount of serum albumin also is a function of its rate of breakdown. The breakdown of serum albumin is complicated by the fact that after oxidation, glycation, or binding of pro-oxidative substances, serum albumin loses its antioxidant capacity and is more rapidly degraded than reduced unbound serum albumin.[79-83] The degradation of serum albumin is influenced by changes in charge and hydrophobicity. In the review of Iwao et al,[82] it was suggested that this probably is affected by endocytosis in the liver, but a receptor has not yet been identified. However, there is evidence in rapidly proliferating cells in cancer that serum albumin can be transported into cells and cell organelles, where it can be degraded to its component amino acids acting as building blocks.[84-88] Finally, in nephrotic syndrome and protein-losing enteropathy, serum albumin is lost via urine or stools, respectively. Taken together, these findings support the possibility that in stressed conditions, the half-life of albumin becomes shorter, in part due to accelerated breakdown. A short half-life of albumin (if present) and increased losses in urine or stools lead to a decrease in total body albumin mass unless compensated by increased synthesis. A comparable mechanism occurs in muscle in stressed states, where protein synthesis increases but degradation increases even more, leading to net muscle efflux of amino acids that serve as building blocks for synthesis of protein and other nitrogen-containing products in wound healing and in the liver and other parts of the immune system. Simultaneously, muscle cells benefit from this response despite net catabolism of muscle mass.[89,90] Total serum albumin mass and the distribution volume of serum albumin determine albumin concentrations in serum, the interstitial space, and in cells. In hypoalbuminemia, the ratio between plasma and interstitial serum albumin mass may be normal at 2:3 or slightly increased.[91] If true, this would imply that a decrease in plasma albumin mass signifies that total serum albumin mass is also decreased. Unfortunately, such a calculation cannot be made because intracellular serum albumin concentrations and transmembrane transport are unknown. In view of the large size of the cellular compartment (>150% of interstitial volume), even low intracellular concentrations may cause large calculation errors. Further study of cell composition and function in the inflammatory state is necessary.

The Benefit of Altered Serum Albumin Kinetics

Much is known in basic science regarding the role of albumin, but in clinical practice, knowledge is generally limited to its role as an oncotic agent and as a presumed indicator of undernutrition. However, scrutiny of the literature reveals that the protein serves several important functions. In blood, serum albumin binds fatty acids; bilirubin; bile acids; calcium, iron (Fe), copper (Cu), zinc, and other cations; drugs; and tryptophan; for an extensive review, see Roche et al.[79] In this way, it may regulate the availability of these substrates and, among other actions, inhibit the pro-oxidative effects of metals and fatty acids.

Albumin is distributed in blood, the interstitium, and in cells. Albumin is considered to be quantitatively the most important extracellular antioxidant, representing almost three-quarters of the antioxidant capacity of plasma.[92] There are 2 main reasons for its antioxidant activity. First, the molecule has strong ligand-binding properties. Important examples of the benefit of the binding properties of albumin are metals like Cu^{++} and Fe^{+++}, which in free form are highly pro-oxidative. They can interact with hydrogen peroxide, leading to the formation of oxygen radicals (hydroxyl radicals), which have deleterious effects. In conjunction with ceruloplasmin, albumin also binds to Cu. Fe binds to transferrin and ceruloplasmin, but has also been demonstrated to be partly bound to albumin. Albumin is also an important ligand of free fatty acids, specifically polyunsaturated fatty acids. Binding prevents peroxidation and the formation of reactive oxygen species. Also, albumin has a free thiol at the Cysteine 34 place, which in free form has a significant capacity to scavenge hydroxyl radicals due to the large albumin pool in the body.[93]

Increased capillary escape of serum albumin may represent a useful mechanism limiting or countering oxidative influences, but also increasing flux of substrate for cell proliferation and deposition of matrix in infection, trauma, and cancer growth. There is evidence that albumin is taken up from the interstitium by rapidly proliferating cancer cells, and is degraded by cell organelles supplying amino acids as building blocks.[86] This especially occurs in nutrient-deprived states and is regulated by mammalian target of rapamycin complex 1 (mTORC1), controlling protein synthesis.[94] Most of the research has focused on cancer cells, but more recently it has been suggested to be a general mechanism also in noncancerous mammalian cells.[87]

Hypoalbuminemic States (see Figure 1)

The different inflammatory states described in the previous section are all associated with low serum albumin levels.[91] Although uncomplicated undernutrition (not combined with inflammation) does not lead to or only very modestly leads to low serum albumin, in areas with endemic malnutrition, undernutrition is usually associated with infectious or noninfectious inflammation. Hypoalbuminemia is more severe in children with kwashiorkor (edema, fatty liver, skin lesions, discolored hair) than with marasmus (less edema, child more active and attentive).[95] The difference in phenotype has been attributed to differences in the microbiome.[96] Chronic parasitic disease or other chronic infections cause hypoalbuminemia and lead to growth failure. Adult malnutrition in areas with endemic malnutrition has similar characteristics.[97] In clinical practice, all acutely ill

or (surgically) traumatized patients have low serum albumin levels.[66-69,98-100] In the Western world, the severity of the inflammatory effects of comorbidity, obesity, lifestyle, organ failure, and aging lead to a proportional decrease in serum albumin levels.[23,76,101-106]

The combined presence of undernutrition and inflammation in malnutrition has led some authors to consider the condition as being a nutrition state caused by a combination of undernutrition and inflammatory activity. Consensus is, however, lacking between countries and nutrition societies about whether inflammation should be part of the definition of malnutrition and part of nutrition assessment.[2,3,107] The frequent and simultaneous presence of undernutrition and inflammation also explains why in some studies a modest correlation has been found between undernutrition and hypoalbuminemia, despite the presence of subgroups, in which undernutrition is associated with normal plasma albumin levels or where low serum albumin levels exist in chronic disease states despite adequate nutrition intake. These observations confound the value of serum albumin as an indicator of adequate nutrition intake or uptake in a sizeable subgroup of individuals despite a significant correlation in the population as a whole.[108] Regardless of how malnutrition is defined, if the objective of the clinician is to identify patients who will benefit from nutrition support, it is essential to consider both undernutrition and inflammation. Only then can the indication for nutrition support be determined and its likely effect be predicted.[109]

The inflammation present in pregnancy is associated with modest hypoalbuminemia, which progresses from the first to the third trimester and is paralleled by increased water content of the maternal interstitium.[30,110,111] Serum albumin levels in healthy children have been found in population studies to be inversely associated with growth rate, although within a range considered normal. The highest serum albumin levels in men are only reached in adulthood after age 20 years, when growth and muscle accretion have stopped. In females, serum albumin levels increase until puberty to levels comparable with men, after which they decrease, although still within the normal range, to below levels in men, possibly related to pubertal growth and subsequent to their menstrual cycle with cyclic tissue synthesis and breakdown.[112]

Hypoalbuminemia and Outcome

Hypoalbuminemia caused by inflammatory activity related to chronic disease or lifestyle (smoking, alcoholism, obesity) is associated with reduced quality of life due to diminished muscle mass and function and cognitive and immune function and, consequently, to diminished life expectancy.[113-116] A decrease in serum albumin levels may result from the inflammatory effects of comorbidity, but very likely also occurs as a result of the aging process itself, which can be considered to be a slow but inevitable inflammatory process caused by the wear and tear of daily life. Different types of chronic comorbidities have a final common pathway of metabolic syndrome, including fatty liver, insulin resistance, dyslipidemia, and atherosclerosis.[117] The same pathway has also been shown to occur in paraodontitis,[118] psoriasis,[119] celiac disease,[120] obesity,[121,122] COPD,[123,124] and rheumatoid arthritis.[125] In all these conditions, hypoalbuminemia develops, and the severity parallels the severity of the inflammatory insult and mortality risk.[25]

Hypoalbuminemia represents a risk factor for medical treatment. It has long been known that patients in intensive care suffering from shock, infection, or trauma react inadequately to a renewed challenge like surgery. This has also been called the phenomenon of the second hit.[126-131] Despite not always appreciating the precise cause of the connection with inflammation, many surgeons know that a low serum albumin level is a bad omen for outcome after surgery.[100,132-138] The problem is apparently due to the preexistent inflammatory state, compromising a further adequate inflammatory response after surgery. To improve outcome, treatment should be directed primarily to decrease inflammation by eliminating the inflammatory cause. This is especially relevant when dealing with infection before embarking on a surgical approach. If this is impossible, eg, in the presence of generalized peritonitis or abscesses, acute surgical intervention is required. However, the surgical approach should be adapted, avoiding extensive oncologic surgery or the construction of hazardous intestinal anastomoses, but instead only trying to achieve "damage control."[100,128,139] This may include drainage of abscesses or removal of infected, damaged, or ischemic tissues. When this approach is successful, nutrition support becomes effective, promoting fat-free mass (muscle) and adequate healing after eventual reoperation, for instance, to restore gastrointestinal continuity and to close the abdominal wall.[100,139] It should be noted that with successful treatment of the cause of the inflammatory response, patients will lose weight due to reduction of edema and to fluid loss, but will regain function. In addition, full recovery and normo-albuminemia will only be reached after months. A restorative reoperation should be postponed at least 6–12 weeks.

The principles described above with regard to the risk of treatment of patients that are already subject to (especially infectious) inflammation, also apply in medical oncology. Hypoalbuminemia often proves to be a strong independent risk factor for failure of chemotherapy and for mortality.[138,140-146]

The strong connection between inflammation and plasma albumin levels will generally make the trend of these levels a suitable instrument to assess improvement or deterioration of the disease process. We closely followed up serum albumin levels in a substantial number of patients with abdominal catastrophe in which damage control was

achieved, but at the expense of open wounds, fistulas, or temporary stomata. This led to the observation that a rise of serum albumin of a few g/L in the course of a week invariably was associated with a negative fluid balance, body weight loss, and clinical improvement, whereas a drop in serum albumin levels was associated with opposite findings. This led to the practice of postponing surgical reintervention at least 6–12 weeks after damage control, when inflammatory activity had significantly subsided and the clinical condition improved, as reflected by the clinical state and increasing serum albumin levels.[100,139]

Other plasma proteins have also been promoted as markers of inflammation. C-reactive protein (CRP) is a true acute-phase protein rising within 10 hours to plasma levels >100 mg/L after major surgery or acute sepsis. CRP is present in very low concentrations in healthy individuals but strongly upregulated, stimulated by IL-6 and NO rising immediately after trauma or infection. There is a close inverse correlation between increases in CRP and decreases in serum albumin levels after 48 hours in well-resuscitated septic or traumatized patients. Thereafter, CRP drops quickly after 3–4 days to low, but still modestly increased, levels if the proinflammatory phase is successful.[147] In this phase, plasma CRP level is primarily an indicator of the severity of the primary insult, initiating innate immunity to clear tissue debris and microorganisms and their products.[148] Thereafter, in the anti-inflammatory phase, CRP is neither a precise indicator of the severity of the metabolic response, nor a very precise indicator of whether there is improvement or deterioration of the clinical state.[147] Only in the presence of renewed or unrelenting tissue damage, CRP will steeply increase or remain strongly elevated. Plasma albumin is a constitutive protein, required in health and disease. After an initial steep drop, plasma albumin levels continue to decrease modestly until 3–7 days after operation, when they start to increase slowly in the case of clinical recovery.[4] Normal levels may only be reached after 3–4 months, reflecting the anti-inflammatory phase promoting wound healing and tissue rebuilding and remodelling.

Effects of Nutrition Support and Serum Albumin Infusion

In the nutrition world, there is an ongoing debate whether inflammatory activity and function should be included in the definition of malnutrition. Although there is agreement that plasma albumin levels reflect inflammation and are a predictor of outcome, the use of serum albumin concentration as an inflammatory indicator is not supported by every nutrition society. Regardless of the outcome of this debate, in clinical practice it is essential to take inflammatory activity (eg, as indicated by hypoalbuminemia) and functional abilities into account because they predict increased risk of medical treatment and, consequently, should influence the art and extent of this treatment.[149] Decreased serum albumin levels are also associated with decreased life expectancy.[25] With increasing severity of inflammation, the effect of nutrition support on muscle protein mass and serum albumin level/synthesis decreases. This is especially relevant in the proinflammatory phase of acute trauma or infection. In this circumstance, it is becoming likely that nutrition support may even delay healing due to potential interference with clearance of damage.[150-152] In the proinflammatory phase, individuals are anorectic and do not tolerate nutrition support well, despite rapidly losing peripheral tissue protein in muscle, skin, and bone. In this case, it is urgent to install instantaneous treatment of the acute trauma or infection that initiates the proinflammatory phase of inflammation. Hereafter, in the anti-inflammatory phase, nutrition support is efficacious, gradually promoting a net positive nitrogen balance at the whole-body level, partly or completely due to rebuilding damaged tissue, while net loss of muscle protein mass is ameliorated. It is not completely clear when muscle, skin, and bone attain a truly positive protein balance. However, when muscle edema decreases, muscle function improves even when muscle size, solids, and composition have not yet regained their pre-illness levels. Complete recovery of peripheral tissues, such as muscle, skin, bone, nails, hair, etc., will take months after the acute trauma or the start of critical illness.

Hypoalbuminemia, associated with chronic disease, reflects inflammatory activity, which induces accelerated loss of muscle mass, above the inevitable loss, shown in study cohorts and starting on average after the age of 30 years. Undernutrition (a negative nutrient balance) and lack of physical exercise accelerate this process. Improving nutrition intake with high protein content and being physically active will, therefore, not completely maintain muscle mass, but will slow down loss of muscle and function.[153] In late stages of the disease process, anorexia, sarcopenia, and inertia are common, which require attention of the caretakers, but are difficult to counter.

The association of low serum albumin with poor clinical outcome raises the question of why no benefit has been achieved by infusion of albumin solutions. An initial Cochrane report suggested that serum albumin infusion might increase mortality.[154] However, other meta-analyses refuted this claim, not finding adverse effects, but also not demonstrating benefit beyond other plasma colloids or balanced electrolyte solutions in adults in the intensive care unit[155-158] as well as in premature babies.[159] More convincing evidence for the benefit of serum albumin infusion has been obtained in patients with tense ascites due to portal hypertension. This may preserve hemodynamic stability, which is at risk after draining substantial volumes of ascites, but increases the risk of extravascular volume expansion.[160]

The many extravascular functions of albumin described in this paper have, to the best of our knowledge, not been

considered as rationale for albumin infusion to replenish a potential deficit. An important measure of adequacy would be the total absolute amount of albumin synthesized in the body in inflammatory states. The likelihood that the turnover time of albumin is shortened in inflammation may lead to a decrease of total serum albumin mass. This would then imply that the increase in the FSR of albumin in serum does not signify that absolute synthesis is increased. In this case, some benefit from albumin infusion might have been expected.

Absence of benefit may depend on the quality of the albumin infused. It is unlikely that pharmaceutical albumin is in its native state as freshly synthesized in the liver. Consequently, the infused albumin may be degraded at an accelerated rate, only serving as an amino acid donor. Moreover, albumin solutions are far more expensive than colloids or balanced salt solutions with similar efficacy, so that without clear evidence of benefit, their use cannot be recommended.

Conclusion

Inflammatory states invariably induce hypoalbuminemia as a consequence of increased capillary escape of serum albumin and other plasma solutes into the interstitium and into cells. This is associated with an increased volume of fat-free mass due to increased total water content of serum, interstitium, and, possibly, cells. In longstanding conditions, blood volume may be normal, but plasma volume increases due to diminished red cell mass. Together, fat-free mass constitutes by far the largest part of the distribution volume of albumin leading to hypoalbuminemia. Whereas the FSR of albumin in plasma is increased in hypoalbuminemia, absolute synthesis rates may not increase due to a shorter turnover time and/or fecal/urinary losses of albumin, which have a lowering influence on whole body albumin mass. As a result, the drop in serum albumin concentration may not be compensated by the increase in the FSR of serum albumin.

An increase in serum albumin FSR appears to be a beneficial response in inflammatory conditions in which an immune response, cell proliferation, tissue healing, and growth are required. Here, albumin plays a scavenging and antioxidative role in the interstitial space. In cells, albumin can also be degraded at an accelerated rate, providing amino acids as building blocks for cell proliferation and matrix deposition.

Low serum albumin levels are, therefore, an indicator of the severity of inflammation. Preexisting inflammation is an important factor interfering with the success of medical and surgical treatment, diminishing the adequacy of the response to trauma and disease and reducing quality of life and longevity. In critical illness, spontaneous rises or decreases in serum albumin levels and the accompanying shrinking (weight loss) or increasing (weight gain) total body water, are valuable indicators, respectively, of recovery or deterioration of health. It is unlikely that low serum albumin levels represent a true deficit and, therefore, albumin infusion is unlikely to be beneficial. Moreover, hypoalbuminemia is not a primary indication for nutrition therapy. The focus of treatment should primarily be directed toward treating the inflammatory cause, although a substantial proportion of hypoalbuminemic individuals are also undernourished and require nutrition support. In the proinflammatory phase of trauma or critical illness, nutrition may not be beneficial, but more research is required.

Statement of Authorship

P. B. Soeters, R. R. Wolfe, and A. Shenkin equally contributed to the conception and design of the research; P. B. Soeters, R. R. Wolfe, and A. Shenkin contributed to the acquisition and analysis of the data; P. B. Soeters, R. R. Wolfe, and A. Shenkin contributed to the interpretation of the data; and P. B. Soeters drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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